Evaluation of Chlorpyrifos as a Toxic Air Contaminant

Consideration of the Addendum

Department of Pesticide Regulation
Human Health Assessment Branch

Scientific Review Panel Meeting
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Presenting today:

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Today's Presentation

- Additional Data or Analysis added per request
- Process for deriving a chlorpyrifos PoD for developmental neurotoxicity from in vivo animal data
- Panel Discussion of Proposed Changes for Final Document
- Review of TAC Authority
- Document Scientific Sufficiency

Additional Data Included in Addendum

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- ✓ Re-analysis of Registrant-submitted FIFRA Guideline Study (Hoberman, 1998)
  - Special emphasis on brain morphology following in utero exposure
  - Pages 6 – 12

- ✓ Thorough analysis of recent in vivo animal studies with developmental neurotoxicity outcomes
  - Carr et al., 2017; Gómez-Giménez et al. (2017, 2018); Lee et al., 2015; Silva et al., 2017
  - Pages 12 – 16 and 54 – 57

- ✓ Additional animal data
  - Primate data (Coulston et al., 1971)
  - Further genotoxic potential evaluation (Muller et al., 2014)
  - Page 16 - 17

Additional Data included in Addendum, continued

- ✓ Most current epidemiological studies added
  - Bulacan, Philippines; Central Ohio; Zhejiang Province, China; Mexico City
  - Critical analysis of quantitative exposure analysis
  - Pages 18 - 24

- ✓ New section on Delayed Neuropathy and Neurodegenerative Effects of Organophosphates added
  - Includes human case reports or epidemiological studies, animal studies, and mechanistic studies for delayed neuropathy, Parkinson's Disease, and Alzheimer's Disease
  - Page 24 - 47

- ✓ New section on additional human effects
  - Includes respiratory effects (pages 48-53) and obesity (page 54)

- ✓ New section on recent advances in PBPK Modeling (page 55)

Additional Data included in Addendum, continued

- ✓ Added two additional age groups to the exposure assessment (infants and children 6 – 12 years old)
- ✓ New analysis of secondary drift exposure estimates
  - Based on DPR Air Monitoring Network data
  - Page 68
- ✓ Re-analysis of house dust data
  - Included new data from Gunier et al., 2016
  - Re-estimation on internal dose from 1999 house dust concentrations and 2006 house dust concentrations for comparison
  - Pages 68-70
- ✓ Revised Dietary Exposure Assessment
  - Updated risk values
  - Pages 71 - 74

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Addendum to the December 2017 Draft Evaluation

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Hazard Identification

Hazard Identification - Introduction

PoD - The dose-response point that marks the beginning of a low-dose extrapolation; can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOEL or LOEL for an observed incidence, or change in level of response.

Critical PoDs established from in vivo animal studies reporting DNT effects at dose levels lower than those that inhibit AChE

Hazard Identification – Study Overviews

- Five recently published studies reported developmental toxicity in rodents (4 rat, 1 mice)
- Oral exposure route (three by gavage, two through the diet)
- Studies were not available to establish dermal and inhalation PoDs for DNT
- Two studies employed both gestational and lactational exposure
- Two studies employed direct pup exposure for either one or seven days starting at PND 10
- Neurodevelopmental responses in offspring were tested either in young pups (PNDs 21-25) or in adults (60-90 days)

Hazard Identification – Study Findings

- Three studies reported increased motor or total activity
- Two studies showed altered anxiety levels (decreased or increased)
- One study detected impaired spatial learning
- In four of studies, the LOEL was the lowest tested dose (0.1-0.5 mg/kg/day)
- Applying an uncertainty factor of 10 to those LOELs would result in an estimated no effect level (ENEL) for DNT of 0.01-0.05 mg/kg/day
- One study included a NOEL based on increased anxiety and motor activity in rats exposed in utero for 6 days (Silva *et al.*, 2017)

Hazard Identification – Study Findings

- Only one study concurrently measured AChE activity
  - LOEL for brain AChE inhibition = 1.0 mg/kg/day (Carr *et al.*, 2017)
- A registrant-submitted FIFRA Guideline Study (Hoberman, 1998)
  - Gestational and lactational exposure
  - RBC AChE inhibition was the most sensitive endpoint in this study with a BMDL10 / BMD10 of 0.03 / 0.06 mg/kg/day
  - HHA set the developmental LOEL at 1 mg/kg/day for brain morphometric changes in PND 66-71 females
  - This LOEL was 10 fold higher than the LOEL for DNT reported in the published studies

Selected Animal Developmental Neurotoxicity Studies

Species, Dosing Period, Doses (mg/kg/day)	Cholinesterase Inhibition				Developmental Neurotoxicity		Study
	Time tested	LOEL NOEL			Effects	LOEL NOEL	
		Plasma	RBC	Brain			
Gestation and postnatal exposure							
Rat; Gavage GD 6-LD 11 0.3, 1.0, 5.0	Dam LD 22	0.3 --	0.06[a] **0.03[b]**	0.65[a] **0.54[b]**	Reduced parietal cortex and hippocampal dimensions in PND 66-71 females	1.0 --	Hoberman, 1998
Rat; Diet GD 7- PND 21 0.1, 0.3, 1.0	Not tested	--	--	--	Decreased spatial learning in 2-3 month old males	0.1 --	Gómez-Giménez et al., 2017
Rat; Diet GD 7- PND 21 0.1, 0.3, 1.0	Not tested	--	--	--	Increased spontaneous motor activity in 2-3 month old males and females	0.1 --	Gómez-Giménez et al., 2018
Gestation-only exposure							
Rat; Gavage GD 14-20 0.01, 0.1, 1.0, 10	Not tested	--	--	--	Increased anxiety and locomotor activity in PND21 males	0.1 **0.01**	Silva et al., 2017
Postnatal- only exposure							
Rat; Gavage PND 10-16 0.5, 0.75 & 1.0	Pups PND 16	--	--	1.0 **0.75**	Decreased anxiety in PND25 males and females	0.5 --	Carr et al., 2017
Mouse; Gavage PND 10 only 0.1, 1.0, 5.0	Pups PND 10	--	--	5.0 --	Increased total activity in PND 60 males	0.1 --	Lee et al., 2015

Hazard Identification – Point of Departure

- A NOEL of 0.01 mg/kg/day based on Silva et al., 2017 for increased anxiety and motor activity in rat pups
  - Supported by applying a 10-fold UF to the LOEL values (in the 4 other studies)
- Exposure duration in the 5 published studies varied from 1 to 35 days
  - Therefore, NOEL of 0.01 mg/kg/day could be applicable to acute and repeated exposures

∴ Acute oral PoD of **0.01 mg/kg/day** used to evaluate acute dermal and inhalation exposures using route-to-route extrapolation

Exposure Assessment

Exposure Assessment

Comprised of two separate parts:

1. Bystander exposure to spray drift from chlorpyrifos applications
2. Dietary exposure to food and drinking water

Exposure Assessment – Bystander Drift

Calculating exposure estimates from:

1) Direct inhalation exposure from airborne chlorpyrifos resulting from pesticide application (1 hr exposure)

2) Incidental oral exposure (non-dietary hand-to-mouth, etc.) from chlorpyrifos that has deposited from spray drift on areas close to treated fields (1.5 hr exposure)

3) Dermal exposure through skin contact with contaminated soil/surfaces (1.5 hr exposure)

4) Combined spray drift exposure (dermal + non-dietary oral + inhalation)

Exposure Assessment – Bystander Drift, continued

We modeled:

- Distances of 25 – 2608 ft from edge of treated field
- Most common and reasonable "worst case" scenarios for application rates and volumes
- Aerial application (fixed wing and rotary)
- Aerial application modeled air concentrations were used as a surrogate for orchard airblast and ground boom

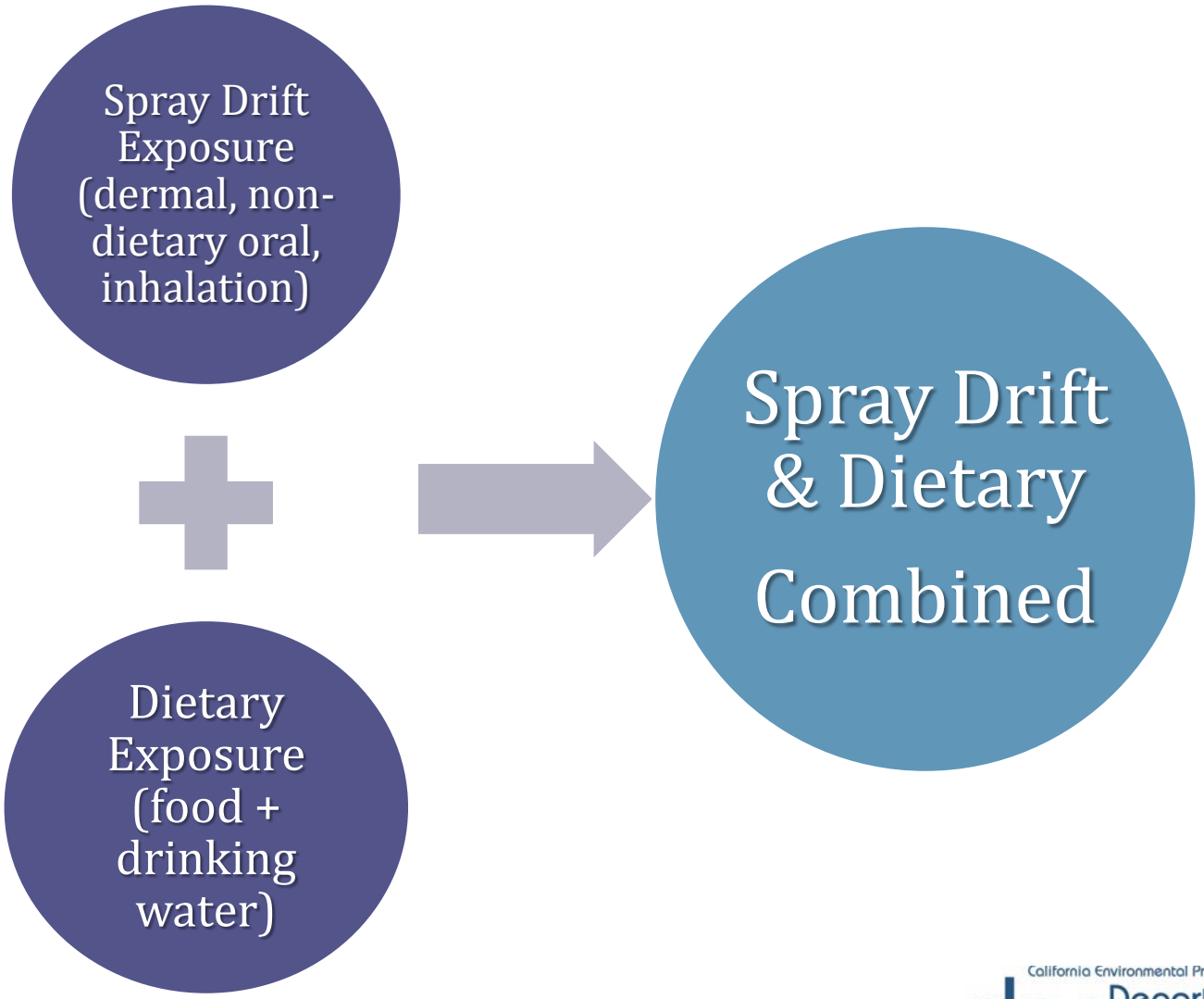
Exposure Assessment – Bystander Drift, continued

- Assessed four age groups
  - Infant
  - Child 1-2 years old
  - Child 6-12 years old
  - Females 13-49 years old
- Estimated absorbed doses for inhalation and dermal routes for MOE calculations
  - For inhalation, assumed 100% external availability and 100% absorption
  - For dermal, assumed 9.6% absorption

Exposure Assessment - Dietary

- Assessed four age groups
  - Infant
  - Child 1-2 years old
  - Child 6-12 years old
  - Females 13-49 years old
- Food (acute and steady state analyses)
  - From all foods with chlorpyrifos registrations
  - 79 individual tolerances and three crop group tolerances
  - Residues based on the USDA Pesticide Data Program monitoring database
  - Consumption based on 2003-2008 NHANES
- Drinking Water
  - Based on DPR measured residues in surface water in CA

Combined Exposure for 1 day



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Margins of Exposure (MOE) from Exposure to Chlorpyrifos for Children 1-2yrs old

	Spray Drift (1- 1.5 hr)				Dietary (1 day)		Combined Exposure
Downwind Distance (ft)	Dermal	Incidental Oral	Inhalation	Spray Drift Dermal+ Oral+ Inhalation	Food	Drinking Water	**Spray Drift + Dietary**
25	2	8	9	1	24	54	1
50	2	10	10	2	24	54	2
100	3	15	13	3	24	54	2
250	7	29	19	5	24	54	4
500	12	54	30	9	24	54	6
1000	31	136	63	21	24	54	9
1320	52	232	92	33	24	54	11
2608	282	1255	279	140	24	54	15

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Pesticide TAC Listing Criteria

Pesticide TAC Listing Criteria

For non-cancer effects, **threshold level is 10x below the air concentration** which has been determined by the director to be protective of human health

California Code of Regulations, Title 3, section 6864

Chlorpyrifos Evaluation as a TAC

TAC defined as air concentrations (modeled or monitored) that exceed the RfC/10

Chlorpyrifos will meet the criteria of listing as a TAC to protect against developmental neurotoxicity through both endpoints, DNT and AChE inhibition:

- ✓ TAC if air concentration **> 0.0005 mg/m³** (500 ng/m³) (Using DNT RfC for children 1-2 yrs of 0.005 mg/m³)

- ✓ TAC if air concentration **> 0.00095 mg/m³** (950 ng/m³) (Using AChEI RfC for children 1-2 yrs of 0.0095 mg/m³)

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Using Modeled Spray Drift Air Concentration (Addendum)

Downwind Distance (ft)	1-hr TWA concentration (mg/m^3)
25	0.0493
50	0.0437
100	0.035
250	0.0237
500	0.0153
1000	0.0072
1320	0.00492
2608	0.00163

Scenario: Child 1-2 yrs with application by fixed wing aircraft with 2 gal/acre spray volume and 2 lbs/acre application rate

Conclusion: Modeled air concentrations at all distances exceeds the RfC/10 (i.e., > 0.0005 mg/m^3 for DNT)

Using Measured Air Concentrations from AMN

Table 2. Summary of ambient Air Monitoring Network results for either Chlorpyrifos or Chlorpyrifos-oxon at Salinas, Shafter, and Ripon during February 2011- December 2014.

Results	Salinas				Shafter				Ripon			
	2011	2012	2013	2014	2011	2012	2013	2014	2011	2012	2013	2014
Average Concentration (ng/m^3)*	7.2	7	4.2	4.2	12.6	15.3	28	22.8	7.3	6.6	7.4	6.5
Maximum 1-day concentration (ng/m^3)*	20.2	20.2	15.5	15.5	28.8	145.6	565.6	447.5	20.2	27.3	20.2	20.2
Maximum 4-week rolling average (ng/m^3)*	13.8	17.9	6.9	6.9	21	54.5	157	124.1	16.1	19.1	12.6	14.4
Number of Non- detects	78	88	105	103	48	54	37	43	75	87	83	89
Number of Trace Detections	16	16	1	1	43	43	60	54	21	16	23	17
Number of Quantitative Detections	0	0	0	0	3	7	9	7	0	1	0	0

* Non detectable concentrations of chlorpyrifos and chlorpyrifos-oxon were substituted with one-half the MDL and trace concentrations were assumed to be the midpoint between the MDL and LOQ.

Conclusion: Max 1-day measured air concentrations at Shafter in 2013 exceeded the RfC/10 in 2013 (i.e., > 0.0005 mg/m^3 for DNT; > 500 ng/m^3)

Source: DPR memo correlating agricultural use with ambient air concentrations of chlorpyrifos during 2011 – 2014 (Budahn, 2016)

Risk Characterization

Risk Characterization

- Risk for threshold effects is expressed as a margin of exposure (MOE)
- MOE = ratio of the critical NOEL or point of departure (PoD) to the estimated human exposure level
- Target MOE for developmental neurotoxic effects is 100
  - 10x for interspecies sensitivity
  - 10x for intraspecies variability
- Critical NOEL = 0.01 mg/kg/d

Route to route extrapolation

- Inhalation and dermal specific NOELs not available (no data to establish)
- Route-to-route extrapolation was performed to convert external dermal dose and inhalation concentrations to internal doses
- Derived acute inhalation and dermal PoDs from oral NOEL

Critical DNT NOELs used for the Risk Characterization of Chlorpyrifos (Table 23)

Route	PoD[a]	RfD[b] or RfC
Uncertainty Factors (UF)		**10 inter 10 intra 1 DNT**
Acute Oral [mg/kg/day] Infants Children 1-2 Children 6-12 Females 13-49	0.01	0.0001
Acute Dermal [mg/kg/day]# Infants Children 1-2 Children 6-12 Females 13-49	0.104	0.001
Acute Inhalation [mg/m^3]# Infants Children 1-2 Children 6-12 Females 13-49	 0.405 0.459 0.624 0.862	 0.004 0.005 0.006 0.009

Margins of Exposure

- Combined spray drift exposures estimates at 2608 feet for dermal, incidental oral, and inhalation routes were combined with the 99.9th percentile exposures from dietary and drinking water for chlorpyrifos
- At 2608 feet from a field treated with chlorpyrifos, the combined spray drift MOEs for all four sensitive population subgroups were at or greater than the target of 100
- However, when dietary and drinking water exposures were added, the aggregate MOEs for these combined routes and sources of exposure were below all the target of 100 (indicating a health concern)

Margins of Exposure using DNT NOEL for Combined Spray Drift, Dietary & Drinking Water (2608ft from Field Edge)

Population Subgroup	Margin of Exposure[a]			
	Diet Only[b]	Drinking Water Only[b,c]	Combined Spray Drift[d]	Combined Spray Drift, Diet and Drinking Water[e]
All Infants < 1 year	37	23	87	12
Children 1-2 years	24	54	140	15
Children 6-12 years	53	87	119	26
Females 13-49 years	67	80	263	32

Abbreviations: DNT = Developmental Neurotoxicity, NOEL = No-Observed-Effect Level.

[a] Margin of Exposure (MOE) = NOEL / Exposure ; DNT NOEL = 0.01 mg/kg/day based on changes in cognition, motor control and behavior in rats and mice (Lee et al, 2015, Silva et al, 2017, Carr et al, 2017, Gómez-Giménez, 2017, 2018)

[b] Dietary exposure estimate at the 99.9th percentile was used in the MOE calculation

[c] Drinking water exposure estimate based on the 99.9th percentile from DPR surface water monitoring was used in the MOE calculation

[d] Combined Spray Drift MOE is the MOE for the combined dermal, incidental oral and inhalation exposure from spray drift at 2608 ft from the treated field which is the only distance where MOEs were greater than 100 for all routes (see Table 24).

[e] Combined MOE = DNT NOEL (0.01) / (Diet + Drinking Water + Combined Spray Drift) Exposure.

Red shading indicates MOEs that are below the target of 100

Proposed additions or edits for final TAC Evaluation Document

For Exposure and TAC determination discussion in Addendum

1. Clearly state how chlorpyrifos can meet the TAC criteria
   - Addition in Risk Characterization, Risk Appraisal, and Conclusion sections
   - Option: reserve discussion on TAC designation for AChE inhibition endpoint in appendix

2. Clearly state how inhalation RfC using DNT endpoint meets TAC criteria - - *however* - - consumption of food and drinking water drive the risk
   - Addition in Risk Characterization, Risk Appraisal, and Conclusion sections

For Discussion of DNT Endpoint in Addendum

1. Move comparison of PoDs and reference concentrations/ doses of developmental neurotoxic effect vs. AChE inhibition to front matter of Appendix 3
2. Revise Executive Summary and Conclusion to focus on DNT
   - Comprehensive analysis of all currently available data to establish a PoD based directly on developmental neurotoxicity

Scientific Sufficiency of the TAC Evaluation

Scientific Review Panel on Toxic Air Contaminants

The Panel shall review "the scientific data on which the report is based, the scientific procedures and methods used to support the data, and the conclusions and assessments on which the report is based."

If SRP determines "the health effects report is seriously deficient," it returns the report to the DPR director who shall revise and resubmit it within 30 days of receiving the SRP's determination of deficiency, and prior to developing control measures or other regulations

Food and Agricultural Code Section14023(b)-(c)

Scientific Sufficiency of the TAC Evaluation

- The report shall assess (FAC § 14023(a)):
  - Availability and quality of data on health effects
  - Potency, mode of action, and other relevant biological factors
  - An estimate of the levels of exposure that may cause or contribute to adverse health effects
  - The range of risk to humans resulting from current or anticipated exposure.

Thank you

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